REMARKS

In the Final Action dated May 12, 2003, Claims 1-21 and 33-66 are pending. Claims 1-21 and 33-44 have been withdrawn from further consideration as being drawn to non-elected subject matter. Claims 45-66 are currently under examination. The amendment filed February 19, 2003, has been objected to under 35 U.S.C. §132 as allegedly introducing new matter. The disclosure has been objected to for certain informalities. Claims 45-66 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support. Claims 57, 62, 65, and 66 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

This response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance or at least in better condition for appeal. Favorable consideration of all pending claims is therefore respectfully requested.

In accordance to the Examiner's requirement, Applicants have cancelled Claims 1-21 and 33-44, without prejudice. Applicants reserve the right to file one or more divisional applications directed to the subject matter of Claims 1-21 and 33-44.

The amendment filed February 19, 2003, has been objected to under 35 U.S.C. §132 as allegedly introducing new matter into the disclosure. Specifically, the Examiner states that the amendment to the specification at pages 30 and 31 indicates that rats were used in the experiments of Example 12. The Examiner alleges that Applicants have not submitted any evidence to verify that rats were employed in the experiments. The Examiner requires that Applicants either cancel the recitation of rats, or provide a declaration confirming that rats were utilized in the experiments of Example 12.

In response, Applicants proffer a declaration (enclosed herewith as Exhibit 1) executed by Dr. John Roderick Morrison ("the Declaration"), in which Dr. Morrison testifies that rats were used in the experiments of Example 12 (see paragraph 9). Accordingly, the objection of under 35 U.S.C. § 132 is overcome and withdrawal thereof is respectfully requested.

The disclosure has been objected to for certain informalities. Specifically, the Examiner alleges that in Example 12, on page 30, at line 18 and page 31, at line 14, the specification refers to "animals" but does not indicate what animal species was used in the Example. In response, Applicants respectfully direct the Examiner's attention to the amendment filed February 19, 2003, which amended the specification to clarify the fact that rats were employed in the experiments described in Example 12. Applicants also submit that Dr. Morrison testifies in the Declaration that rats were used for experiments in Example 12 (see paragraph 9 of the Declaration). Accordingly, the objection is overcome and withdrawal thereof is respectfully requested.

The Examiner has also alleged that, in the table in Example 13 on page 32, the first column heading reads "transfected embryonic fibroblast," but there is no guidance regarding what was used to transfect the fibroblast. With respect to the amendment filed February 19, 2003, regarding the use of a construct comprising a *lacZ* gene to transfect the fibroblasts, the Examiner further alleges that nothing in the specification suggests the transfected fibroblast in Example 13 carried the *lacZ* gene. In response, Applicants respectfully direct the Examiner's attention to the Declaration of Dr. Morrison, in which Dr. Morrison testifies that the transfected fibroblasts used in Example 13 carried the *lacZ* gene (see paragraphs 10 and 11 of the Declaration). Accordingly, the objection is overcome and withdrawal thereof is respectfully requested.

Claims 45-66 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support for reasons as applied to Claims 22-32 in the previous Official Action.

The Examiner acknowledges that the claims are directed to (i) a method of producing a non-human embryo by nuclear transfer, using a neural stem cell as the source of the donor nucleus, (ii) a method of producing a genetically modified non-human animal by nuclear transfer, and (iii) a method of producing a cell line from an embryo to produce cloned cells of an embryo.

However, the Examiner alleges that "there is no basis for jumping to the conclusion that methods of cloning by nuclear transfer are applicable to all animals." In doing so, the Examiner cites Westhusin et al. (Theriogenology 55: 35-49, 2001), which discloses that "without a doubt, one of the major factors influencing the probability of cloning a specific animal is species." The Examiner states that isolation and propagation of neural stem cells (NSCs) are not at issue here. The Examiner also alleges that there is no support for the statement that basic techniques for nuclear transfer are the same across different species. The Examiner further alleges that there is no support for the statement that difficulties encountered in cloning various species could be overcome by routine experimentation or by transferring reconstructed embryos to recipient animals without first culturing them. Moreover, the Examiner alleges that there is no support that the procedures used in the rat can readily be used in other species. Specifically, the Examiner indicates that no cloned rat has been reported as of the filing date of the present application. Furthermore, the Examiner alleges that the specification does not teach how to use an embryo for anything other than for producing a cloned animal.

In the first instance, Applicants respectfully submit that an embodiment of the present invention is the isolation, culturing and propagation of the NSCs and the use such NSCs for cloning purposes. Thus, the use of NSCs for cloning purposes of the present invention is premised on a protocol for isolating and propagating the NSCs in all mammalian species.

Applicants observe that Westhusin et al. merely state that species is one of the factors influencing the probability of cloning a specific animal. Westhusin et al. do not teach that there is any major difference in nuclear transfer steps in a cloning procedure. In fact, Westhusin et al. disclose that the basic approach involving nuclear transfer is similar and includes six steps (in all animal species). Westhusin et al. teach that the techniques that are required to accomplish each of these steps vary slightly between species. (See Westhusin et al. at page 36 paragraph 4).

Thus, Applicants submit that Westhusin et al. merely teach the difference in the ease of cloning a particular animal (by adjusting specific parameters). These specific or optimum parameters can be achieved by one of ordinary skill in the art. While it may take time for one in the art to adjust conditions for the maximum cloning efficiency, the quantity of such routine experimentation does not approach the undue experimentation standard for a proper enablement rejection. In addition, Applicants respectfully direct the Examiner's attention to Exhibits B and C attached to Exhibit 1, enclosed herewith. Exhibits B and C provide further evidence of successful nuclear transfer experiments in rat, mouse and bovine models, which involved the same technical approaches as illustrated in Examples 1-5 of the present specification. Moreover, Dr. Morrison confirms that the nuclear transfer procedures are the same in all three species. For example, the procedures described in Exhibits B and C involve oocyte enucleation; introduction of the neural stem cell nucleus; activation of the oocyte to initiate embryonic development and culture *in vitro* to the morula/blastocyst stage (see the Declaration,

paragraph 14). Dr. Morrison also confirms that the results outlined in Exhibits B and C demonstrate that the description and enablement of the technology in one mammalian (i.e. rat) species by the present invention serves as a validation of the approach in all other species. (see the Declaration, paragraph 15). Accordingly, the features of the present invention are clearly applicable to species other than rat.

With respect to the enablement rejection based on references cited in the previous Office Action which purportedly teach that the potential of enucleated oocytes receiving somatic cells to develop into young *in vivo* varies among species, Applicants submit that, in addition to the arguments submitted in the previous response, the Westhusin et al. reference cited by the Examiner also supports Applicants' argument that nuclear transfer procedures have little or no variance among species. For example, Westhusin et al. disclose that the basic approach involving nuclear transfer is similar and has six steps (in all animal species). Westhusin et al. teach that the techniques that are required to accomplish each of these steps will only vary slightly between species.

Moreover, Applicants direct the Examiner's attention to a publication by Hirabayashi et al., enclosed herewith as Exhibit 2, which outlines the problems inherent in the *in vitro* manipulation of rat oocytes and embryos. Specifically, Hirabayashi et al. indicate that the failure of nuclear transferred rat embryos to develop into full-term offspring is due to microinjection of cell nuclei into oocytes that have spontaneously activated (see Page 35, paragraph 2 of Hirabayashi et al.). As indicated by Hirabayashi et al. and according to Applicants' own findings, the reportedly difficulty in adapting nuclear transfer procedures to the rat is due to the spontaneous activation of the rat oocyte *in vitro*, which reduces the efficiency with which donor nuclei can be reprogrammed and the subsequent development to the

morula/blastocyt. Applicants submit that further optimization of the rat nuclear transfer procedures is required to overcome this propensity, such as using an agent to block the spontaneous activation (see Josefsberg et al., enclosed herewith as Exhibit 4). Applicants submit that, despite these perceived inefficiencies, Applicants have for the first time demonstrated that NSC nuclei are capable of directing rat embryo development into the morula stage (see the Declaration at paragraph 14).

Regarding the transfer of reconstructed embryos directly to recipient animals as opposed to culturing them *in vitro* for a period before transfer, Applicants respectfully direct the Examiner's attention to a publication by Papaioannou et al. (abstract enclosed herewith as Exhibit 3) which describes the use of the mouse oviduct as an improved culture environment for early mouse embryos (see the abstract of Papaioannou et al.). Applicants submit that this is a standard approach used by embryologists to overcome developmental problems that may be introduced by *in vitro* culture. Applicants submit that this approach in rat cloning will only address the efficacy between the *in vitro* culture conditions for rat embryo development and the *in vivo* culture system.

Moreover, in an effort to expedite favorable prosecution, Applicants have canceled Claims 63-66, without prejudice. Applicants reserve the right to file a divisional application to the subject matter of Claims 63-66.

In view of the foregoing, Applicants submit that one skilled in the art can make and use the present invention without undue experimentation. Accordingly, the rejection of Claims 45-66 under 35 U.S.C. § 112, first paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 57, 62, 65, and 66 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Specifically, the Examiner indicates that Claim 57 is indefinite in its recitation "2 to 20 μ/ml" because a μ is a unit of measurement for length rather than mass. In response, Applicants submit that the recitation "2 to 20 u/ml" in Claim 57 was a typographical error. Applicants have amended Claim 57 by reciting "2 to 20 ug/ml." Support for the amendment to claim 57 is found throughout the specification, and in original Claim 37, for example.

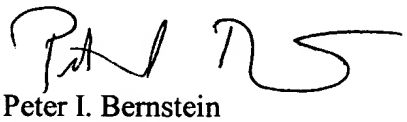
The Examiner also alleges that Claim 62 is indefinite in its recitation of "destroying" and "deleting" because it is unclear how "destroying" would be distinguished from "deleting." The Examiner requires that clarifying claim language is needed in Claim 62. The Examiner agrees that a "deleted" gene is one that has been removed, but his does not distinguish "deleting" from "destroying."

In response, Applicants have amended Claim 62 by replacing "destroying" with "inactivating." Support for the amendment can be found throughout the specification and particularly at page 6, lines 15-21, page 23, lines 1-5, for example. In addition, the definition of such terms are commonly used in the art, e.g., by textbooks and popular reference books, such as Wu, et al., *Methods in Gene Biotechnology*, CRC Press, 1997, on pages 343-344, for example. As indicated above, claims 63-66 have been cancelled without prejudice.

Accordingly, the rejection of Claims 57, 62, 65, and 66 under 35 U.S.C. §112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, the present application is in condition for allowance which action is earnestly solicited.

Respectfully submitted,



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PIB/ZY:ab/lf/yd
Encl.: Exhibit 1 (includes Exhibits A-C)
Exhibit 2
Exhibit 3
Exhibit 4